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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,817	09/17/2003	Barry Reisberg	1049-1-034N	3446

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EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,817	REISBERG, BARRY	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,15-26,28,31-45,47,50-59,61 and 64-70* is/are pending in the application.

4a) Of the above claim(s) *1-7,10,15-22,31-42,45,50-55,64-66 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-9,23-26,28,43-44,47,56-59,61,67,69-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10, 15-26, 28, 31-45, 47, 50-59, 61 and 64-70 are presented for examination.

Applicant's Amendment filed May 30, 2006 has been received and entered into the application. Accordingly, claims 8, 26, 43 and 67 have been amended.

Claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, 67 and 69-70 are under examination and claims 1-7, 10, 15-22, 31-42, 45, 50-55, 64-66 and 68 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) and the requirement for restriction dated May 17, 2005.

Applicant's arguments, filed May 30, 2006, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, 67 and 69-70 remain rejected under 35 U.S.C. 112, first paragraph, because the specification fails to reasonably provide enablement for the treatment of Alzheimer's disease or other degenerative cognitive diseases, such as age-associated memory impairment, mild cognitive impairment or cerebrovascular dementia, insofar as Applicant has defined "treatment" to encompass "the identification of treatment populations at

risk for a neurodegenerative condition, e.g., prior to development of MCI, Alzheimer's disease or cerebrovascular dementia" (see present specification at paragraph [0022] at pages 6-7), for the reasons already made of record at pages 5-13 of the previous Office Action dated January 25, 2006, of which said reasons are herein incorporated by reference.

Applicant's remarks have been carefully considered in their entirety, but fail to be persuasive.

First, it is here reiterated that the present rejection was set forth to show a lack of sufficient enabling disclosure for the aspects of "treating" that Applicant has defined as identifying populations of at risk for a neurodegenerative condition prior to development of a neurodegenerative condition, e.g., prior to development of MCI, Alzheimer's disease or cerebrovascular dementia, or arresting or reversing the progression of the process and/or disease. The aspect of simply "treating", in the sense of ameliorating, or making better, the signs and symptoms that characterize these neurodegenerative diseases does not lack sufficient enabling disclosure.

In response to the rejection set forth under 35 U.S.C. 112, first paragraph, Applicant states that, "Applicant intends that 'treatment' include amelioration of symptoms and/or slowing of progression of the condition. For instance, 'treatment' (amelioration) of symptoms includes a reduction of cognitive disability, a reduction of functional disability, and a reduction of behavioral disturbances." (see page 15 of Applicant's remarks)

However, this assertion is directly contrary to the manner is which the term "treatment" has been defined in the accompanying disclosure. Applicant defines the term "treatment" at paragraph [0022] at page 6 of the disclosure, which states, "By the term 'treatment' is meant the

administration of medicine to ameliorate AAMI, MCI, Alzheimer's disease, CVD or a related neurodegenerative condition in a patient suffering from such a condition or affliction. Amelioration of the condition includes slowing the progression of the process and/or disease, arresting the progression of the process and/or disease, or reversing the progression of the process and/or disease. A specific aspect of the instant invention is the identification of treatment populations at risk for a neurodegenerative condition prior to development of a neurodegenerative condition, e.g., prior to development of MCI, Alzheimer's disease or cerebrovascular dementia." Such a definition clearly encompasses embodiments of the invention that circumscribe methods of prevention, given that Applicant is identifying patients *prior to development of a neurodegenerative condition*, i.e., those that are, thus, asymptomatic, and are considered at risk for developing such a condition and thereby thwarting the development of such a condition.

Applicant argues against the basis of the rejection by citing numerous references in support of the position that Alzheimer's disease is actually a disease that is amenable to diagnosis and that definitive diagnosis based on clinical manifestations during the patient's lifetime can actually be made. While such is not disputed by the Examiner, the evidence provided by Applicant does not speak to the issue of identifying patients considered at risk *prior to development of such a neurodegenerative condition.* Applicant has failed to provide any evidence, or describe any protocol, either in the present disclosure or accompanying remarks, that may be used to identify patients that are otherwise asymptomatic for any neurodegenerative disease as those that are highly likely to develop such a condition in the future.

It is here noted that the evidence cited in the rejection by the Examiner (i.e., Cecil's Textbook of Medicine, Gauthier et al., Greicius et al. and Gasparini et al.), and even those references cited by Applicant, fully support the assertion that diagnosis, though it may be, to some extent, speculative until post-mortem confirmation, can at least be made during a patient's lifetime based upon the clinical and pathophysiological manifestations of the disease. However, there is no art-accepted protocol for the determination of patients considered at risk but do not show symptoms of the disease. To reiterate the discussion from the previous Office Action of January 25, 2006, this cannot even be accomplished via cerebrospinal fluid testing or genetic testing. Cecil's Textbook of Medicine states, "CSF evaluation for amyloid protein and tau protein can increase the likelihood of a diagnosis of Alzheimer's disease, but they are not sufficiently specific to be of routine value in screening or early diagnosis of Alzheimer's disease...Presence of the apoE4 allele makes it very likely that the patient's dementia is produced by Alzheimer's disease. ApoE testing does not have predictive value for asymptomatic individuals." (see "Diagnosis", column 2 at page 2044) Even the early stages of Alzheimer's disease are common complaints of aging or result from other neurological conditions, such as depression, where memory impairment is not present (see "Evaluation of Dementias", column 1 at page 2042).

The lack of any established correlation between the clinical presence of biological or genetic markers commonly associated with, and could be construed as being predictive of, Alzheimer's disease, or any definitive distinction between what is considered the normal aging process and what is considered predictive of neurodegeneration, casts significant doubt on the predictability of the art of determining those patients at risk for such a condition. It is in this

circumstance that one must consider whether Applicant has demonstrated sufficient enabling disclosure in the specification to overcome this unpredictability in the art such that one of ordinary skill in the art would be able to use the disclosed invention commensurate in scope with the claimed subject matter, namely, for the identification of patients at risk for a neurodegenerative condition *prior to the development of such a condition.*

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Given that the art clearly and unambiguously recognizes the unpredictability of determining patients who are at risk and asymptomatic, the artisan would have required sufficient direction or guidance as to how this aspect of the invention could actually be achieved, since the lack of predictive value of biological or genetic testing in asymptomatic individuals is sufficiently unpredictable so as to preclude a common, art-accepted protocol for the identification of patients at risk. However, the specification does not provide such direction or guidance. The present disclosure is simply directed towards the "treatment", in the sense of ameliorating or making better, of these neurodegenerative diseases, but does not address this aspect of identifying those patients who are at risk for developing such a condition *prior to the*

development of such a condition. Though it is once again acknowledged that the Office does not require the presence of working examples to enable the disclosure of the invention, the lack of any working or prophetic examples further speaks to the fact that Applicant has conspicuously failed to provide any discussion or guidance as to how this aspect of the invention would actually be practiced.

In light of such, it is maintained that one of ordinary skill in the art would be faced with the impermissible burden of undue experimentation in order to accomplish this embodiment of the invention. The basis for the rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice this aspect of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

It is clear from the discussion above and referencing the discussion set forth in the previous Office Action, that the state of the art with regard to the identification of patients at risk for developing neurodegenerative diseases *prior to the development of such a condition(s)*, is highly unpredictable. The amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification needs more detail and guidance as to how to use the invention in order to be enabling. Please reference *In re*

Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) and *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). Applicant fails to address the unpredictability by providing adequate direction or guidance as to how to practice this aspect of the invention, in terms of disclosing how patients at risk could be identified, what criteria would be used to determine such patients and how such patients at risk would be treated using the presently claimed combination of agents such that the skilled artisan would have been imbued with at least a reasonable expectation of success in identifying and treating patients *prior to developing a neurodegenerative condition* such that the incidence of actually developing such a condition would be, in the broadest reasonable interpretation (see MPEP §2111.01), 0% and could be reasonably expected not to occur. As a result, the specification is viewed as lacking an enabling disclosure of the same.

For these reasons, rejection of claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, 67 and 69-70 under 35 U.S.C. 112, first paragraph, remains proper and is **maintained**.

Claim Rejections - 35 USC § 112, Second Paragraph (New Ground of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-9, 43-44, 47 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 8, 43 and 67 have been amended to now recite "other retrogenic diseases". However, it is noted that Applicant has failed to set forth in a reasonably clear, deliberate or

precise manner what diseases would be included or excluded from the phrase "other retrogenic diseases" such that the skilled artisan would have been reasonably apprised of the metes and bounds of the claimed subject matter and would have been able to readily determine what would constitute infringement of the present claims.

Disclosure pertinent to the claimed genus of "other retrogenic diseases" is found at page 7, paragraph [0023] of the specification and states, "By the term 'related retrogenic diseases, 'related dementias', 'related neurological conditions and disorders', and the like, is meant neurological conditions that present some degree of degeneration from the normal adult neurological condition. This includes measurable decline of normal cognitive, neurologic, or functional capacity. Decline in normal neurological capacity can be determined by any method known to the art, including the global deterioration scale (GDS)...and/or the functional assessment staging (FAST) procedure....".

However, such disclosure does not provide a limiting definition as to what other diseases are considered "retrogenic diseases" other than those expressly named in the claims, i.e., Alzheimer's disease, age-associated memory impairment, mild cognitive impairment or cerebrovascular dementia, such that the skilled artisan would have readily understood what diseases were encompassed by such a term. Words and phrases in the claims must be given their "plain meaning" as understood by one having ordinary skill in the art unless defined by Applicant in the specification with "reasonable clarity, deliberateness or precision" (MPEP §2111.01). Here, Applicant's description of those diseases that are considered "other retrogenic diseases" is not reasonably clear, deliberate or precise because the definition does not specifically delineate what diseases are considered "retrogenic" and defines such diseases in a

relative way, as compared to normal neurological function. However, what is considered "normal" is a subjective interpretation and is highly variable between subjects, such that what may be considered "abnormal" in one person and, thus, indicative of retrogenic disease, may not be considered abnormal in another person and, thus, would not be considered indicative of retrogenic disease. In other words, absent any limiting definition of the phrase "other retrogenic diseases", this aspect of the claims is open to subjective interpretation as to what diseases are included or excluded from such a term and, therefore, fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, 67 and 69-70 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan (WO 02/020022; March, 2002) in view of Lipton (WO 92/17168; 1992), Lee et al. (U.S. Patent No. 6,043,224; 2000), Gervais et al. (U.S. Patent Application Publication No. 2005/0031651; Published 2005, Priority to U.S. Provisional Patent Application No. 60/482,214, filed June 2003) and Morris et al. ("Mild Cognitive Impairment Represents Early-Stage Alzheimer's Disease", 2001), each already of record, for the reasons already of record at pages 15-30 of the previous Office Action dated January 25, 2006, of which said reasons are hereby incorporated by reference.

Applicant's remarks have been carefully considered in their entirety, but fail to be persuasive.

Applicant addresses each of the references to Duncan (WO 02/020022), Gervais et al. (U.S. Patent Application Publication No. 2005/0031651), Lipton (WO 92/17168) and Lee et al. (U.S. Patent No. 6,043,224) individually, but does not provide any discussion regarding the combination of references as they were set forth in the rejection under 35 U.S.C. 103(a) to support the *prima facie* case of obviousness. Applicant states that each discrete reference to Duncan, Gervais et al., Lipton and Lee, when taken alone, does not teach all of the elements of the presently claimed invention.

Such arguments are not persuasive. It must be remembered that the references are relied upon in combination when set forth under 35 U.S.C. 103(a) and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references that make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the combination of the cited references as previously discussed at pages 15-30 of the Office Action dated January 25, 2006. Please reference *In re Young*, 403 F.2d 754, 159 USPQ 725 (CCPA 1968) and *In re Keller* 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Rejections under 35 U.S.C. 103(a) are based on combinations of references, where the secondary references are cited to reconcile the deficiencies of the primary reference with the knowledge generally available to one of ordinary skill in the art to show that the differences between Applicant's invention and the prior art are such that they would have been modifications that were *prima facie* obvious to the skilled artisan. *The claimed invention is not required to be*

expressly suggested in its entirety by any one or all of the references cited under 35 U.S.C. 103(a). Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Additionally, it is noted that although Applicant may have been motivated to combine the three elected agents for a different reason than that provided in the previous Office Action, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. Please see the reasoning in *In re Kerkhoven*, 205 USPQ 1069 (CCPA) as to the obviousness of combining two or more agents known to be used in the prior art for the same therapeutic indication(s). See also *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Conclusion

Rejection of claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, 67 and 69-70 remains proper and is **maintained**.

Claims 1-7, 10, 15-22, 31-42, 45, 50-55, 64-66 and 68 remains **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Leslie A. Royds
Patent Examiner
Art Unit 1614

August 4, 2006

Ardin H. Marschel 8/5/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER